

## Case Report

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# PD-1/PD-L1 inhibitors combined with chemotherapy in the treatment of thymic carcinoma metastasis to the liver

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### Abstract

Epithelial neoplasms of the thymus is a relatively rare malignancy. In this report, we present a case of thymic carcinoma of a 68-year-old man with hepatic metastasis, which with the severe hypokalemia, hypoproteinemia, and fatigue of concomitant symptom. After positive symptomatic treatment such as correction of electrolyte disorder, supplementation of albumin and nutritional support, the patient's general condition recovered and improved. Then, we reviewed the literature on the treatment of thymic carcinoma, and decided to use immunotherapy combined with chemotherapy to treat this case of advanced thymic squamous carcinoma, expecting to have a good efficacy and improve the progression-free and overall survival.

**Keywords:** Thymic carcinoma; Chemotherapy; Immunotherapy.

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### Background

Thymic epithelial neoplasms include thymoma, thymic carcinoma and neuro-endocrine. Rare, they nevertheless represent 20% of all mediastinal tumors and 50% of those located in the anterior mediastinum, with very few extrathoracic spread [1]. Thymic carcinoma is more aggressive than thymoma, and accounts for about 15% of the incidence of thymic tumors [2]. The most common histological types of thymic carcinoma are squamous cell carcinoma, lymphoepithelial carcinoma, undifferentiated carcinoma and so on. Complete surgical resection with postoperative adjuvant radiotherapy and chemotherapy is preferred for surgically resectable thymic epithelial neoplasms. Radiotherapy and chemotherapy are the main treatments for advanced unresectable thymic epithelial neoplasms, but there

is a lack of standard treatment. In recent years, targeted therapy drugs and immune checkpoint inhibitors have shown certain therapeutic prospects in thymic carcinoma.

For advanced or metastatic thymic carcinoma, platinum-based combination chemotherapy should be used to shrink the tumor and alleviate the associated symptoms. At present, the standard chemotherapy regimens are still uncertain, but paclitaxel + carboplatin is the first choice for the first-line chemotherapy of thymic carcinoma, and fluorouracil/tetrahydrofolate, gemcitabine/capecitabine, paclitaxel, pemetreuse, etoposide, isophoramide and so on, can be selected for the second-line chemotherapy [3]. There is a lack of effective evidence-based medical evidence for targeted therapy of thymic carcinoma, but the new drugs in the study include everolimus, sunitinib and

others [4]. Further, some studies have shown that patients with higher PD-L1 expression in thymic carcinoma have better efficacy after receiving immunotherapy [5,6].

In this case report, we present a patient with liver metastasis who had no indication for surgery. Then, he was treated with Camrelizumab that is the PD-1 immunotherapy combined with Paclitaxel for Injection and carboplatin, which showed a good therapeutic effect.

### Case report

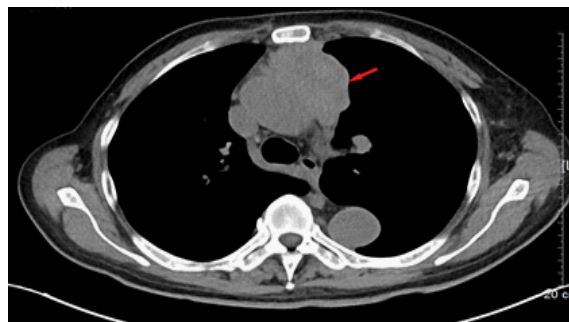
A 68-year-old man who developed poor, fatigue, and emaciation for 4 months, was not attention to treatment. He was admitted to the emergency department because his symptoms gradually worsened and he developed nausea, vomiting, and difficulty swallowing. Emergency whole-abdominal CT examination revealed multiple liver lesions with a diameter of about 67 mm for the larger one, which enhanced scan showed ring enhancement, so it was considered as a metastatic tumor (Figure 1).



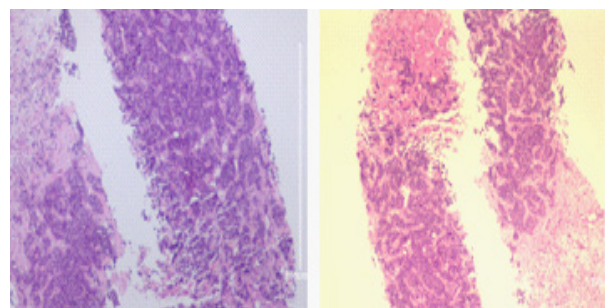
**Figure 1: Abdominal Computed Tomography (CT).** Multiple mixed density masses of different sizes (red arrow) were found in the liver. The largest one was about 67 mm in diameter.

After admission, the patient was further examined by chest CT, and then found a soft tissue mass in the anterior mediastinum which uneven density and fuzzy edge of mass, disappearance of local and perivascular space. The size of the tumour was about 37 mm X 69 mm, which accompanied by multiple lymph node enlargement in the anterior mediastinum, left neck root, clavicular and left axilla (Figure 2).

Subsequently, a coarse needle biopsy of the liver mass was performed, which indicated that the liver tissue was infiltrated by malignant tumor. Combined with immunohistochemical results, the liver metastasis of squamous cell carcinoma was consistent with thymic carcinoma (Figure 3). Immunohistochemistry investigations demonstrated the carcinoma cells were positive for CD5, CD117, P40, CK5/6, P53 and Ki-67 (50%), and negative for other immunomarkers (CK20, CK7, CEA, GPC3, Villin, PSAP, NapsinA, CgA, Syn) in the panel, which supported the diagnosis of a metastasis from a primary thymic carcinoma rather. Associated tumor marker tests suggested that only the level of CYFRA was higher, while the other markers were within the normal range (Figure 4).



**Figure 2: Chest Computed Tomography (CT).** The mediastinum was in the middle, and there was a soft tissue density mass (red arrow) in the anterior mediastinum with uneven density and fuzzy edge, and the local and perivascular space disappeared, which the size was about 37 mm X 69 mm and the CT value was about 26-44HU. Multiple lymph node enlargement was observed in the anterior mediastinum, left neck root, suclavicular and left axilla.

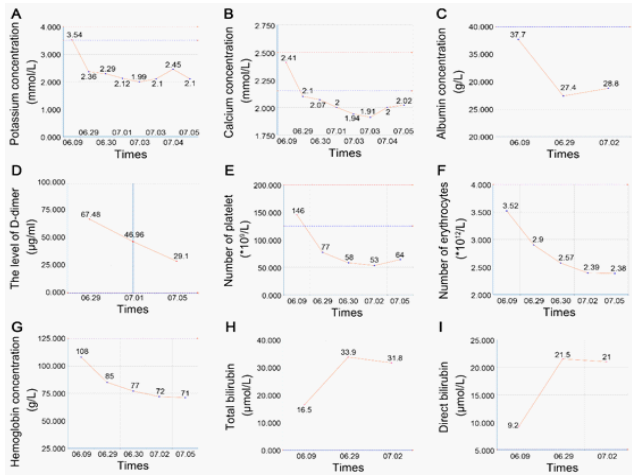


**Figure 3: Pathological results of coarse needle biopsy of liver mass.** Microscopic examination of the liver biopsy tissue showed the malignant tumor cells infiltrating the liver tissue, consisting of squamous cell carcinoma.

Abbreviations	Project name	Specimen type	Results	Unit	Reference range
CEA	Carcinoembryonic antigen	Serum	1.340	ng/ml	< 4.70
CA125	Carbohydrate antigen 125	Serum	32.60	U/ml	≤35
CA199	Carbohydrate antigen 199	Serum	10.3	U/ml	≤35
CA724	Carbohydrate antigen 724	Serum	< 1.500	U/ml	< 6.9
CYFRA	Cytokeratin-19-fragment	Serum	57.50	ng/ml	< 3.3
AFP	Alpha fetoprotein	Serum	4.79	ng/ml	< 7.00

**Figure 4: Tumor markers.** Carcinoembryonic antigen, carbohydrate antigen 125, carbohydrate antigen 199, carbohydrate antigen 724, Cytokeratin-19-fragment, alpha-fetoprotein and other markers were detected

After diagnosis, the patient's physical condition was always poor, with persistent hypokalemia, hypocalcium and hypoproteinemia, and then gradually hapened the anemia, elevated bilirubin and hypercoagulability (Figure 5). We corrected the electrolyte disturbances (more than 10 g of potassium every day), and supplemented albumin and blood transfusions boosted the immune function. Furthermore, low-molecular-weight heparin sodium injection was given as anticoagulant, and bilirubin was reduced, and more hepatocyte function was protected. Then, the patient was stabilized and started on albumin-bound paclitaxel and carboplatin combined with the PD-1 inhibitor Camrelizumab for therapy.



**Figure 5:** Relevant serological tests. Potassium concentration, calcium concentration, albumin concentration, hemoglobin concentration and the number of erythrocyte, the level of bilirubin and the coagulation function were detected

## Discussion

Thymic carcinoma is a rare mediastinal malignancy caused by thymic epithelial cells, with an incidence of 0.13 to 0.32 per million [7]. Thymic carcinoma tends to occur in adult males over the age of 50 [8]. The most common histopathological types are squamous and undifferentiated carcinoma. Many thymic carcinoma patients were initially diagnosed with invasion or metastasis, usually involving surrounding organs or metastasized to mediastinal lymph nodes, pleura, lung, pericardium and so on [9]. Few thymic carcinomas are found only on physical examination without any clinical symptoms.

The onset of thymic tumor is insidious, and the first symptoms of patients are often local mediastinal compression symptoms, such as chest tightness, shortness of breath, head and face swelling, dyspnea, severe cough and so on. In addition, when the tumor compresses the sympathetic nerve, it can cause ipsilateral blepharoptosis, pupil narrowing, enophthalmos, frontal apperspiration, and Horner syndrome. Hoarseness can be caused when the tumor compresses the recurrent laryngeal nerve. And superior vena cava obstruction syndrome can be occurred when it is compressed. One third of thymomas are associated with autoimmune diseases [10], most of which are related to anti-acetylcholine receptor antibodies, including myasthenia, aplastic anemia and hypoproteinemia [11].

This patient's initial symptoms were abdominal discomfort and digestive tract symptoms, mainly due to thymic carcinoma metastasize to the liver. Afterward, he developed severe electrolyte disturbances, hypoproteinemia and anemia, which is consistent with the autoimmune symptoms associated with thymoma.

Study reported that about one-third of patients with thymic carcinoma were initially diagnosed with lymph node or distant metastasis [12], which often metastasize to liver, bones, lung, pleura or lymph nodes.

P53 is one of the most important tumor suppressor genes discovered so far, whose mutation can lead to dysregulation of cell apoptosis, uncontrolled cell proliferation and tumgenesis, and suggest a poor prognosis [13,14]. Ki-67 is a nuclear protein that can be used as a marker of cell proliferation [15,16], and its index is closely related to the degree of differentiation, in-

vasion, metastasis and prognosis of many tumors. In this case, p53 expression was positive and the positive Ki-67 staining was more than 50%, which suggest that this patient's thymic carcinoma is more aggressive and capable of distant metastasis.

The standard treatment for thymic carcinoma has not been established and its prognosis is poor. Clinical experience suggests that paclitaxel and carboplatin are the first choice for chemotherapy. At the same time, PD-1/L1 immunotherapy for thymic carcinoma was found to have significant clinical benefits [17-19]. Katsuya et al. reported a phase II study of Nivolumab in 15 patients with unresectable or relapsed thymic carcinoma, including 13 patients with squamous cell carcinoma, which subgroup analysis showed a median PFS of 3.8 months and an OS of 14.1 months [20]. Studies have found that the expression level of PD-L1 are reported to be higher in thymic carcinoma than in thymoma, but it remains unclear whether the expression level of PD-L1 predicts the prognosis of thymic carcinoma [21]. Albumin-paclitaxel is based on paclitaxel and added albumin as a carrier, which has better efficacy and fewer adverse reactions. Therefore, this patient was treated with albumin-paclitaxel and carboplatin for chemotherapy, and combined with Camrelizumab for immunotherapy.

## Declarations

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**Conflict of interest:** The authors declare that they have no conflict of interest.

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